## REMARKS

Claims 1-20 and 23-33 are pending in the application. Claims 1, 3, 12, 14, 23, and 25 have been amended herein. Claims 34-51 have been added herein. Thus, after entry of these changes, claims 1-20 and 23-51 will be pending in the application.

Claims 1, 12, and 23 have been amended to correct punctuation, to remove the phrase "which down-regulates expression of", and to indicate that the oligonucleotide is complementary to nucleic acid encoding the N-terminal 8-13 codons of protein kinase A subunit RIα and having from 0 to 25 additional nucleotides extending from the 3′ terminus, the 5′ terminus, or both the 3′ and 5′ terminus. Support for these amendments is found in the specification at, *inter alia*, page 5, lines 7-18; Table 1, page 22; page 22, line 3 to page 23, line 3; and page 63, lines 11-12. Accordingly, no new matter has been added by these amendments. Claims 3, 14, and 25 have been amended to delete the word "essentially." This amendment has been made to expedite prosecution and does not indicate that Applicant has acquiesced to the Examiner's comments regarding the cancelled subject matter. Support for new claims 34-51 can be found generally throughout the specification and the original claims, including, *inter alia*, in the specification at page 5, lines 7-18; Table 1, page 22; page 8, line 13; page 9, lines 18-29; and page 23, lines 3-9. Accordingly, no new matter is added by these claims.

Applicant assumes that all rejections not repeated in the Office Action of January 29, 2003, have been overcome and are withdrawn.

The outstanding rejections are addressed individually below.

***1. Pending claims are enabled by the specification as filed.***

Claims 1-20 and 23-33 stand rejected under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification as filed.

Claim 1 as amended is directed to a method for inhibiting proliferation of cancer cells comprising administering to the cells a first agent comprising a synthetic, modified oligonucleotide complementary to nucleic acid encoding the N-terminal 8-13 codons of protein kinase A subunit RIα and having from 0 to 25 additional nucleotides extending from the 3′ terminus, the 5′ terminus, or both the 3′ and the 5′ terminus, and wherein the oligonucleotide is a hybrid, inverted hybrid, or inverted chimeric oligonucleotide of specific characteristics, and administering to the cells a second agent comprising an antibody that binds to EGFR or a cytotoxic agent selected from an enumerated group, wherein the administering steps may be performed simultaneously or sequentially in any order. Other independent claims are directed to a pharmaceutical composition, a method for treating cancer, and to these various methods and compositions in which the oligonucleotide is complementary to at least 15 consecutive nucleotides of the nucleic acid encoding the N-terminal 8-13 codons of protein kinase A subunit RIα.

The Office Action states that the specification, while being enabling for inhibiting proliferation of cancer cells *in vitro*, and for inhibiting the proliferation of cancer cells *in vivo* and treating cancer in a subject comprising the administration of HYB 165, does not reasonably provide enablement for treatment of cancer in a patient *in vivo* comprising the administration of all synthetic modified oligonucleotides complementary to protein kinase A subunit RIα. (Office Action, page 2) The Office Action further states that at the time of filing of the instant application, neither the prior art nor the specification as filed provided sufficient guidance to use a synthetic modified oligonucleotide, other than HYB 165, to treat cancer in an afflicted subject, wherein the sequence of the oligonucleotide is complementary to a portion of PKA subunit RIα other than the sequence to which HYB 165 is complementary (noting that the oligonucleotide according to HYB 190 is complementary to the same portion of PKA RIα as HYB 165). (Office Action, page 2)

The claims have been amended to recite that the administered oligonucleotide is complementary to nucleic acid encoding the N-terminal 8-13 codons of protein kinase A subunit RIα. This is the nucleotide sequence to which HYB 165 (SEQ ID NO:4), cited by

the Examiner to be enabled, is complementary. This language is supported in the specification at, *inter alia*, page 63, lines 11-12 (the first two lines of the "Materials" section of Example 13), which states "HYB 165, a 18-mer mixed backbone oligonucleotides (MBO) targeted against the N-terminal 8-13 codons of the human RIα regulatory subunit of PKA, . . . ." The sequences listed in Table I (page 22) indicate that HYB 166 (SEQ ID NO:6) and HYB 190 (SEQ ID NO:1) are complementary to the same region of PKA RIα as HYB 165 (SEQ ID NO:4), which the Examiner has indicated is enabled.

This action does not indicate that Applicant has acquiesced to the Examiner's rejection of the cancelled subject matter, as Applicant reserves the right to prosecute these unamended claims in a continuation application.

Furthermore, as has been discussed in responses to previous office actions, the specification provides examples indicating that the invention works as claimed.

The oligonucleotides of the invention have been tested *in vitro* in a variety of cell types, both with and without the second agent. The specification indicates that *in vitro* experiments were performed analyzing, *inter alia*, the effect of inverted hybrid or inverted chimeric structure on oligonucleotide-mediated mitogenicity (page 50, line 16 to page 52, line 6) and to determine the ability of inverted hybrid oligonucleotides and inverted chimeric oligonucleotides to activate RNase H *in vitro* when bound to a complementary RNA molecule (page 56, line 4 to page 57, line 28). Furthermore, Examples 13-26 (pages 63-89) describe *in vitro* experiments using oligonucleotides (HYB 165) of the invention, both with and without the second agent, in a variety of different cellular environments including ZR-75-1 human breast cancer cells, GEO human colon cancer cells, 1AP, 1A9PTX22 and 1A9PTX10 human ovarian cancer cells, and OVCAR human ovarian cancer cells.

Additionally, the claimed invention has in fact been tested and found to work *in vivo*. Applicant again directs the Examiner to Examples 27, 28, and 29 (pages 90-95) as well as Figures 16, 17, and 18 of the instant patent application, which provide examples

and data indicating that the claimed invention does work *in vivo* in an accepted animal model. More specifically, Example 27 indicates that HYB 165 inhibits tumor growth after intraperitoneal or oral administration in mice. The data for this experiment is presented in Figures 16A and 16B. Example 28 indicates that oral HYB 165 cooperatively inhibits tumor growth and increases survival in combination with taxol. Data for this experiment is presented in Figures 17A and 17B. Example 29 indicates that the cooperative antitumor effect of HYB 165 with taxol is accompanied by inhibition of new vessel formation and growth factor production as well as other results of histochemical analysis. Data for this experiment is presented in the table in Figure 18. Additional support for the *in vivo* use of the methods and pharmaceutical compositions of the invention is found in the description of the figures in the specification at page 20, lines 9-29.

Additionally, Example 10 indicates that a single dose of RIα antisense, hybrid (Oligo 165; SEQ ID NO:4), or inverted hybrid (Oligo 166, SEQ ID NO:6) oligonucleotide was tested by injection into the right flank of athymic mice previously innoculated with tumor cells and tumor volumes were obtained (page 58, line 25 to page 59, line 20) and the results are shown in Figure 1. Thus, several oligonucleotides of the invention were tested *in vivo*.

Furthermore, Tortora *et al.*, (1997) *Proc. Natl. Acad. Sci. USA* **94:**12586-12591, attached Appendix A to the Amendment filed November 4, 2002, was previously cited by the Examiner and referred to in the Rule 132 Declaration filed March 26, 2001. This reference indicates that HYB 190, an inverted chimeric oligonucleotide corresponding to SEQ ID NO:1, combined with paclitaxel, significantly increased tumor growth inhibition as compared to untreated mice or to mice treated with each single agent. This reference was cited by the Examiner under 35 USC § 102(a), and therefore must have been considered by the Examiner to show enablement.

Thus, hybrid, inverted hybrid, and inverted chimeric oligonucleotides complementary to the nucleic acid encoding the N-terminal 8-13 codons of protein kinase A subunit RIα have been shown to work *in vivo*. Furthermore, the hybrid and

inverted chimeric oligonucleotides have been shown to work cooperatively with a second agent according to the invention.

Accordingly, Applicant has shown successful correlation between *in vitro* and *in vivo* studies in Examples 27, 28, and 29, as well as in Example 10 with the use of protein kinase A subunit RIα specific oligonucleotides in an established, art accepted mouse model. In addition, mouse models have been used as acceptable animal models for cancer treatment for years. In fact, one of skill in the art would be aware that mouse models are the "standard" animal model for taking a drug into a clinical setting, including for cancer treatment. These results and the art at the time of filing suggest that *in vitro* results are predictive of *in vivo* use for inhibiting proliferation of cancer cells and that the oligonucleotides of the invention work *in vivo*.

Thus, Applicant respectfully asserts that the Examiner's concerns regarding *in vivo* use are inappropriate.

Additionally, Applicant notes that the Office Action discusses the language "consisting essentially of" in the context of a 35 U.S.C. § 112, first paragraph, enablement rejection. It is unclear to Applicant whether these claims are also being rejected under 35 U.S.C. § 112, second paragraph. In order to facilitate prosecution of this application, the word "essentially" has been removed from the claims.

Therefore, Applicant submits that in view of the foregoing remarks and the references submitted, pending claims 1-20 and 23-51 are enabled by the specification as filed.

Accordingly, Applicant respectfully requests that the rejection of these claims under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

## CONCLUSIONS

In view of the arguments set forth above, Applicant respectfully submits that the rejections contained in the final Office Action mailed on January 29, 2003, have been overcome, and that the claims are in condition for allowance. If the Examiner believes that any further discussion of this communication would be helpful, she is invited to contact the undersigned at the telephone number provided below.

Applicant encloses herewith a Petition for a One Month Extension of Time pursuant to 37 C.F.R. § 1.136 up to and including May 29, 2003, to respond to the Examiner's Office Action mailed on January 29, 2003. Please charge deposit account no. 08-0219 the $55.00 fee for this purpose.

The Commissioner is authorized to charge deposit account no. 08-0219 the $270.00 fee for the new claims added herein (3 additional independent claims and 16 unpaid-for claims in excess of 20).

No other fees are believed to be due in connection with this response. However, please charge any underpayments or credit any overpayments to Deposit Account No. 08-0219.

Respectfully submitted,

Ann-Louise Kerner, Ph.D.
Reg. No. 33,523

**Date: May 29, 2003**

HALE AND DORR LLP
60 State Street
Boston, MA 02109
Tel: (617) 526-6000
Fax: (617) 526-5000